REMARKS

After entry of this amendment, claims 1-21 are pending, of which claims 4 and 17-20 are withdrawn. New claim 21 has been added and finds support *inter alia* in the original claim 1. The claims have been amended without prejudice or disclaimer to better comply with the U.S. practice, to correct antecedent basis, and to address various points made in the Office Action. Support for the amendment is found *inter alia* in the original claims. Further support for the amended claim 1 is found in the specification at page 4, lines 15-19. No new matter has been added.

Claim Objections

Claims 1, 10-11, and 14-16 were objected to for improper recitations. Claim 14 was further objected to for lack of antecedent basis. It is believed that the objection is rendered moot in light of the present amendment. Reconsideration and withdrawal of the objections is respectfully requested.

Claim Rejections – 35 USC § 112, Second Paragraph

Claims 1-3 and 5-16 were rejected under 35 U.S.C. § 112, second paragraph, for being indefinite due to the use of improper recitations, improper Markush language, and missing step(s). In view of the present amendment, it is believed that the rejections are rendered moot. Reconsideration and withdrawal of the rejections is respectfully requested.

Claim Rejections – 35 USC § 112, First Paragraph

Claims 1-3 and 5-16 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement and lack of an enabling disclosure. Applicants respectfully disagree. However, to expedite prosecution, claim 1 has been amended without prejudice or disclaimer to recite the nucleotide sequence with more specificity. Applicants respectfully submit that claim 1 as amended overcomes both rejections.

Written Description Rejection

The Examiner alleges that the specification describes only the sequence of SEQ ID NO: 1 encoding SEQ ID NO: 2, but not other amino acid sequences that would have Δ-4-desaturase activity. The Examiner further alleges that the specification fails to disclose any specific

structural features that define an amino acid sequence having Δ-4-desaturase activity. Applicants respectfully disagree that the claims as amended are not described.

As amended, claim 1 specifies the nucleotide sequence to be the sequence of SEQ ID NO: 1, a nucleotide sequence encoding the polypeptide sequence of SEQ ID NO: 2, or a nucleotide sequence encoding a polypeptide sequence having at least 95% homology at the amino acid level with SEQ ID NO: 2. It is respectfully submitted that the specification provides sufficient written description for the claimed genus as defined by the amended claim.

As noted by the Examiner, the specification describes the sequence of SEQ ID NO: 1 that encodes SEQ ID NO: 2. Because the genetic code and its redundancies were known in the art at the time of filing, the disclosure of SEQ ID NO: 2, combined with the pre-existing knowledge in the art, would have put one in possession of the genus of nucleic acids that encodes SEQ ID NO: 2. With the aid of a computer, one skilled in the art could have identified all of the nucleic acids that encode a polypeptide with at least 95% homology with SEQ ID NO: 2. Thus, one of ordinary skill in the art would conclude that Applicants were in possession of the claimed genus at the time the application was filed. See, "Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, 'Written Description' Requirement," at page 37-38.

Furthermore, as described in the specification at page 4, line 33 through page 5, line 2, natural variations (*e.g.* DNA sequence polymorphisms) can lead to alterations in the amino acid sequences of the Δ-4-desaturase within a population, bringing about a variation of 1-5% in the nucleotide sequence of the Δ-4-desaturase gene without altering the functional activity of the Δ-4-desaturase. Accordingly, the claim scope created by the recitation of at least 95% homology with SEQ ID NO: 2 includes the expected range of natural polymorphic variants, which should certainly within the scope of the invention.

Moreover, other desaturase enzymes were known in the art at the time of filing, including Δ-4-desaturases isolated from *Thraustochytrium* and *Schizochytrium*. Thus, consensus domains or motifs common to most or all desaturases were known to those skilled in the art. For instance, it is known in the art that desaturases generally contain cytochrome b5-like domain, including the heme-binding motif (HPGG), and three histindine-rich motifs. The presence of these domains/motifs in SEQ ID NO: 2 could be easily identified. See, *e.g.*, Meyer *et al.*

(Biochemistry, 2003, 42: 9779-9788, cited in IDS dated November 16, 2005), page 9784, paragraph bridging left and right columns. These conserved domains suggest guidance as to common structures. Accordingly, it is respectfully submitted that the claims as amended satisfy the written description requirement, since there is clearly a correlation between the written description and the amended claim scope. Reconsideration and withdrawal of the rejection is respectfully requested.

Enablement Rejection

The Examiner further rejects the claims for lack of enablement, alleging that the specification does not enable any nucleic acid encoding the variants or homologs of SEQ ID NO: 2. Applicants respectfully disagree.

As disclosed in the specification, a Δ-4-desaturase may be modified by substitution, inversion, insertion or deletion of one or more amino acid residues while retaining the desired function. See page 8, lines 14-35. For instance, such a modification can be realized by replacing one amino acid with another amino acid having similar physicochemical properties (*e.g.*, bulk, basicity, or hydrophobicity). See page 8, lines 20-21. From this guidance, a person skilled in the art would be directed to mutations which are not likely to impair function. Methods of generating such mutations, for example, site-direct mutagenesis and PCT-mediated mutagenesis, are standard techniques readily available and known to those skilled in the art. The need for routine screening to confirm function is normal in the art and not undue experimentation.

Furthermore, as disclosed at pages 24-32, the specification provides detailed guidance including working examples on how to clone a Δ-4-desaturase gene (Example 3), how to clone an expression plasmid for heterologous expression in yeasts (Example 4) or plants (Example 5), and how to test its activity in producing the desired product in yeast (Examples 7-9). Additionally, the specification discloses a sequence alignment between SEQ ID NO: 2 and the Δ-4-desaturase from *Thraustochytrium* (Figure 2). One skilled in the art would know to avoid introducing any substitution or modification in regions that are highly conserved among those sequences. In view of the detailed description, guidance, working examples, and high level of skill, the specification enables the full scope of the claim without undue experimentation. On

these facts, an analysis under *In re Wands* supports enablement. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

This analysis is in consistent with the Board's decision in *Ex parte Kubin*, 83 USPQ2d 1410 (B.P.A.I. 2007) (hereinafter " Kubin"), where the Board held that a claim encompassing 80% amino acid sequence identity to the disclosed sequence was fully enabled. *Kubin* at 1416. As the Board noted in *Kubin*, even though practicing the full scope of the claims might have required extensive experimentation, the experimental techniques were well-known in the art, so the experimentation would have been routine and thus, not undue. *Id.* at 1416.

As in *Kubin*, the experimentation required to practice the present claims (making and screening mutant sequences) is routine in nature and clearly not "undue." For instance, variants can be screened in yeast for function, as illustrated in Example 7, which is clearly not undue experimentation. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner further alleges that the specification is enabling only for transforming a nucleic acid encoding SEQ ID NO: 2 into yeast and using such transformed yeast for the production of polyunsaturated fatty acids by feeding with DPA, but not for any nonhuman organism in which the claimed Δ-4-desaturase will function or the culture conditions required for use of the claimed nucleic acid to produce polyunsaturated fatty acids. Applicants respectfully disagree with the Examiner's characterization and conclusions.

It is initially noted that, as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 USC § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970); see also M.P.E.P. § 2164.01(b). Accordingly, Applicants respectfully submit that the enablement rejection based on this ground should not be applied to the claims directed to a nucleic acid sequence, a gene construct, or a vector.

Furthermore, it is noted that the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. See *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure); see also

M.P.E.P. § 2164.04. As discussed above, the specification provides working examples on how to generate a transgenic nonhuman organism such as yeast or a plant that expresses a Δ-4-desaturase gene. See, *e.g.*, Examples 5 and 6. The specification further provides detailed guidance concerning producing transgenic plants at pages 17-21. Thus, the specification provides not only examples, but also sufficient guidance for one skilled in the art to generating expression constructs, producing transgenic nonhuman organisms, and expressing the construct resulting in the production of the desired polyunsaturated fatty acids in nonhuman organisms. The feeding experiment as illustrated in Example 7 is designed to demonstrate the enzymatic activity as well as the substrate specificity of the Δ-4-desaturases of the present invention. See page 28, lines 32-34. One skilled in the art, after reading the disclosure, would expect that polyunsaturated fatty acids would be produced in a transgenic nonhuman organism expressing the Δ-4-desaturases of the present invention when DPA is either exogenously supplied to or endogenously produced by the organism. For instance, Δ-4 fatty acid desaturase substrate such as 22:5 (n-3) substrate can be exogenously supplied to a plant which transgenically expresses a Δ-4-desaturase as demonstrated in WO 02/26946 (see Example 9 at page 48). Accordingly, there is no reason to doubt the operability of the claimed subject matter. Simply pointing to the absence of working examples does not meet the initial burden to question enablement, since the presence/absence of working examples is only one factor considered in assessing objective enablement. *In re Wands, supra.*

For at least these reasons and in light of the present amendment, it is respectfully submitted that the claims recite a scope of subject matter which a skilled artisan could clearly make and use according to the teaching in the specification. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejection – 35 USC § 103(a)

Claims 1-3 and 5-16 were further rejected under 35 USC § 103(a) as being obvious over Mukerji *et al.* (hereinafter "Mukerji"). Applicants respectfully disagree and traverse the rejection for the following reasons.

To support a *prima facie* conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. *In re Lowry*, 32 F.3d 1579, 1582, 32 USPQ2d 1031,

1034 (Fed. Cir. 1994); see also *Ex parte Alexander*, 86 USPQ2d 1120, 1122 (BPAI 2007) (where the Board reversed the obviousness rejection in part because the Examiner had not identified all the elements of the claim).

As acknowledged by the Examiner, Mukerji teaches Δ-4-desaturases having less than 40% identity with SEQ ID NO: 2. Thus, Mukerji does not disclose or suggest a nucleic acid encoding a polypeptide having at least 95% homology with SEQ ID NO: 2.

The Examiner alleges that it would have been obvious to one skilled in the art to isolate other Δ-4-desaturase coding sequences from other organisms, such as from an algal species, for the purpose of producing polyunsaturated fatty acids in a transgenic organism as taught in Mukerji. The Examiner further asserts that cloning multiple fatty acid biosynthetic genes into one single construct would have been merely a matter of choice. Applicants respectfully disagree with the Examiner's characterization and conclusions.

As mentioned above, the Δ-4-desaturases taught in Mukerji have less than 40% identity with SEQ ID NO: 2. Even assuming *arguendo* that one skilled in the art would have been motivated to search for other Δ-4-desaturases from other organisms, the art does not predict that polypeptides having only very low homology would have the same enzymatic activity. Thus, the rejection is based on an "obvious to experiment" type of approach and no success was predictable.

Moreover, the enzymatic activity of the claimed Δ-4-desaturases is superior to that of the known Δ-4-desaturase. As demonstrated in Table 1 of the specification (page 30), the Δ-4-desaturases of the present application shows a more-than-double enzymatic activity as compared to the Δ-4-desaturases disclosed in Mukerji. For instance, 29.7% of omega-3-DPA (22:5 Δ7,10,13,16,19) was converted by the Δ-4-desaturases of the present application (see Table 1, row 2) while only 15.3% was converted by the Δ-4-desaturases taught in Mukerji (see Table 7 of Mukerji, row 6) in a feeding experiment using transgenic yeast. Likewise, 28.7% of ADA (22:4 Δ7,10,13,16) was converted by the Δ-4-desaturases of the present application (see Table 1, row 3) while only 11% was converted by the Δ-4-desaturases taught in Mukerji (see Table 7 of Mukerji, row 5). Accordingly, by this additional reason, the Δ-4-desaturases of the present application would not have been obvious in view of the cited prior art.

For at least the above reasons, the subject matter of the pending claims would not have been obvious. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

For at least the above reasons, Applicants respectfully request withdrawal of the rejections and allowance of the claims.

Applicants reserve all rights to pursue the non-elected claims and subject matter in one or more divisional applications.

Accompanying this response is a petition for a two-month extension of time to and including September 7, 2008, to respond to the Office Action mailed April 7, 2008 with the required fee authorization. No further fees are believed due. If any additional fee is due, please charge our Deposit Account No. 03-2775, under Order No. 12810-00136-US from which the undersigned is authorized to draw.

Respectfully submitted,

By /Hui-Ju Wu/
Hui-Ju Wu, Ph.D.
Registration No.: 57,209
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
(302) 658-5614 (Fax)
Agent for Applicants

#604045